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(19)

(54) IMPROVEMENTS IN OR RELATING TO CONTAINERS OF ANTISEPTICS FOR THE TREATMENT OF BURNS AND SCALDS

(71) We, WILKINSON SWORD LIMITED, a British Company, of Sword Works, Southfield Road, London, W.4, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to containers for dispensing antiseptics for the treatment of burns and scalds.

When a subject has been injured so that a relatively large area of a limb, the trunk, or the face is in a wounded condition, it is frequently very difficult to treat the injured area, because of the direct mechanical difficulties of applying and keeping in place a suitable dressing, and because of the normally encountered extreme sensitivity of the patient to any pressure on the wounded or the adjacent area. This is particularly so with some severe burns and scalds. In spite of these difficulties, it is the normal practice to provide a dressing, a prime function of which is to inhibit infection of the wound.

The present invention provides a container of antiseptic for the treatment of burns and scalds by topical application, containing a topically acceptable antiseptic active agent *Pseudomonas aeruginosa*, a pressurising agent and at least one surfactant admixed with water, said container comprising an outlet, and valve means operable to allow discharge of the contents of the container through said outlet in the form of a foam which is effective in the control of *Pseudomonas aeruginosa* at the site of a burn or scald.

By the term "surfactant" we mean compounds having surface active properties, the term including soaps and synthetic surfactants.

The present invention enables an aerosol foam to be dispensed which overcomes the above difficulties, because the foam will stay in place on the injured area and will remain effective for several hours, giving not only an effective control as aforesaid but also a barrier against air-borne infection. In addition, little or no pain is caused by the application of the foam, or during its removal which is easily effected by washing in a gentle stream of water.

According to one embodiment of the invention the antiseptic in the foam is a salt of α - amino - ρ - toluene - sulphonamide. Preferably the salt is a water soluble salt such as an acetate, hydrochloride, lactate, or tartrate.

We find that the α - amino - ρ - toluenesulphonamide cation produces insoluble materials by reaction with the anionic species of soaps and that the formation of these materials gives rise to poor foam properties, valve blockage, and also reduces the antiseptic action of the foam. Although such a foam is of use in some instances, it is of restricted value. We find that no such deleterious reaction occurs with a suitable soapless composition, and that a soapless composition containing 0.5 to 5.0% by weight of a salt of α - amino - ρ - toluenesulphonamide such as the acetate, hydrochloride, lactate or tartarate, produces an antiseptic foam of good properties. Further, in those instances where long shelf-life or a controlled pH are desirable, the soapless composition may be kept in one compartment of the container and an aqueous solution of a salt of α - amino - ρ - toluenesulphonamide in a second compartment. The foam produced on actuation of the valve has a pH which can be pre-controlled within narrow limits over a wide range. Similarly, the use of two-compartment contains with soaps alleviates some of the problems, such as intermittent actuation, encountered in a premixed soap composition, but in general it does not provide the particularly effective foam produced by a soapless composition where the soapless composition and the aqueous salt solution are stored separately.

Thus, the invention further provides a

container of antiseptic for the treatment of burns and scalds by topical application, comprising a first compartment containing a pressurising agent and at least one surfactant admixed with water, a second compartment containing a topically acceptable antiseptic active against *Pseudomonas aeruginosa* or a substance which will react with a substance contained in said first compartment to form a desired antiseptic, said second compartment containing a pressurising agent and/or being collapsible under the pressure of the pressurising agent contained in said first compartment, an outlet from the container, and valve means operable to put both compartments in communication with the outlet, operation of said valve means resulting in discharge from said outlet of a foam containing an antiseptic which is effective in the control of *Pseudomonas aeruginosa* at the site of a burn or scald.

According to a further embodiment of the invention the antiseptic in the foam is 5 - nitro - 2 - furaldehyde semicarbazone. This antiseptic is incorporated readily into a foam-base containing a soap, but the resultant composition, although effective, has a limited shelf-life. It is believed that the relatively high pH value required for soap-containing compositions gives rise to decomposition of the 5 - nitro - 2 - furaldehyde semicarbazone. The drawback, whatever its cause, is overcome by use of a two-compartment container, with the 5 - nitro - 2 - furaldehyde semicarbazone in one compartment, dissolved and/or dispersed in an aqueous medium which preferably contains a dispersing agent such as a long chain polyoxy-alkylated alkyl ether and/or a protective colloid such as hydroxyethylcellulose or sodium carboxymethylcellulose, with the other compartment containing either a soapless or a soap-containing composition. Likewise, we find that the use of a soapless composition with 5 - nitro - 2 - furaldehyde semicarbazone directly dispersed or dissolved in the composition, at a pH of about 7.2 to 7.8, or even lower, results in a final composition of improved shelf-life. All the compositions containing 5 - nitro - 2 - furaldehyde semicarbazone are preferably formulated so that the dispensed foam contains 0.05 to 1.5% by weight of 5 - nitro - 2 - furaldehyde semicarbazone.

In yet another embodiment of the invention the antiseptic in the foam is the silver salt of 2 - sulphanilamidopyrimidine. Although this salt may be incorporated directly as a dispersion into a soap-containing or soapless composition, the container has a limited life; not only does the silver salt of 2 - sulphanilamidopyrimidine appear to react with constituents of the compositions or to decompose, but also the metal components of the aerosol unit in contact with the mixture undergo undue corrosion processes.

This problem can be overcome by the use of a dual compartment container of the kind referred to above in which the silver salt is contained in one compartment in aqueous suspension, preferably in conjunction with a protective colloid, and a soap-containing or, preferably, a soapless composition is stored in the other compartment.

An alternative solution is a container of antiseptic for the treatment of burns and scalds by topical application comprising a first compartment containing a salt of 2 - sulphanilamidopyramidine, a pressurising agent and at least one surfactant admixed with water, a second compartment containing a silver salt, at least the lining of said second compartment being non-reactive to silver ions, said second compartment containing a pressurising agent and-or being collapsible under the pressure of the pressurising agent in said first compartment, an outlet from the container and valve means operable to put both compartments in communication with the outlet, operation of said valve means resulting in discharge from said outlet of a foam containing a silver salt of 2 - sulphanilamidopyrimidine which is effective in the control of *Pseudomonas aeruginosa* at the site of a burn or scald.

An aqueous solution of a silver salt, such as the nitrate or acetate, is stored within one compartment, and the 2 - sulphanilamidopyrimidine, preferably in a quantity representing a 10—50% molar excess over the silver ion, is stored in solution as a salt, such as a sodium or potassium or triethanolammonium salt, in the other compartment which also contains a soap-containing, or preferably, a soapless composition, the silver salt of 2 - sulphanilamidopyrimidine being formed when the contents of the two compartments react on discharge.

All the compositions containing the silver salt of 2 - sulphanilamidopyrimidine are preferably formulated so that the dispensed foam contains about 0.2 to 4.0% by weight of the antiseptic compound.

In another embodiment of the invention the antiseptic is a silver compound capable of ionising to provide argentous ions. However, the direct incorporation of soluble silver salts into a soap-containing composition can give rise to difficulties, such as corrosion of the container and valve blockage. The use of a two-compartment container with a solution of the silver salt, such as the nitrate or acetate, in one compartment, reduces the difficulty. However, a preferred embodiment is one in which a solution of the silver salt, such as the nitrate or acetate, is stored in one compartment with a soapless composition in the other compartment.

The direct inclusion of a silver salt into a soapless composition provides a suitable foam, but the shelf-life of the unit is limited.

All the compositions containing the argentous ion, other than in conjunction with 2 - sulphanilamidopyrimidine, are preferably formulated so that the dispensed foam contains about 0.02 to 2.0% by weight of silver in chemical combination as a salt.

In those cases where a silver compound is present in a two-compartment container, the use of a valve which contains no metal components in contact with the silver compound is desirable.

Suitable pressurising agents are hydrocarbon mixtures such as butane, isobutane and propane, in weight proportion to the total contents of the container of from 3.5% to 4.5%, or fluorocarbons in weight proportion to the total contents of the container of from 7.0% to 10.5%. Whereas a mixture of dichlorodifluoromethane and dichlorotetrafluoroethane in weight ratio of 40:60 is preferred, equivalent molar proportions of other fluorocarbon propellants may be used.

One example of a two-compartment container will now be described, by way of example only, with reference to the accompanying drawing in which:

Figure 1 is a sectional side elevation of the container, and

Figure 2 is a view similar to Figure 1 of the upper part only of the container in the discharging position, the container normally being inverted when dispensing.

Referring to the drawing it will be seen that the container comprises a body 10 which at its upper end carries a valve assembly 11. The valve assembly 11 comprises a tubular dispensing nozzle 12 of plastics material whose lower half has sealed to it a valve 13 of resilient material which in turn is sealed to a dished metal cap 14 whose periphery is secured in the mouth of the body 10. The dispensing nozzle 12 carries a disc 12a at its lower end which, near its periphery, has five holes 12b extending therethrough (only two of which are shown in the drawing). These holes 12b are normally closed at their upper end by the rim 13a of the skirt of the valve 13. Three holes 12c (only two visible in the drawing) are provided in the lower end of the nozzle 12. A flexible bag 15 sealed to the rim of the disc 12a provides an inner compartment.

The pressurising agent and the surfactant admixed with water are stored in the body 10 and the antiseptic is stored in the bag 15. The pressure in the body 10 tends to compress the bag 15, but the constituent within the bag 15 cannot escape because of the closure of the holes 12b at their upper end by the valve 13.

When the composition is to be dispensed, the nozzle 12 is tilted and this causes a part of the upper face of the disc 12a to separate from the rim 13a of the valve 13. Consequently one or more of the holes 12b are no longer sealed by the rim 13a, and the constituent within the bag 15 is forced out into the space under the skirt of the valve 13 where it mixes, in proportions determined by the geometry of the valve, with the second constituent entering in the direction of the arrow A. The mixed constituents enter the nozzle 12 through one or more of the holes 12c and are ejected as a mixture from the outer end of the nozzle 12. At atmospheric pressure the pressurizing agent expands to a gas and a foam is produced in the form of a dispersion of gas bubbles in a liquid matrix.

Soap-containing compositions other than those specified in the examples below may be used and we find that the following composition is particularly valuable for some applications. Foams based on the composition have been applied to many severe burns on humans, with no discomfort to the patient.

Lauric acid	3.0%
Stearic acid	7.0%
Sodium carboxymethylcellulose, (British Celanese, P.75)	0.2%
Potassium hydroxide	2.2%
Sodium lauryl sulphate	3.0%
30% aqueous solution of Cocodimethylamine - N - oxide, *(Aromox) ("Coco" refers to the mixture of fatty acids obtainable from coconut oil)	10.0%
Water to 100%.	
Packed as aqueous solution,	95.9 parts
Butane, propellant,	4.1 parts.

*Aromox is a registered trade mark

Soapless compositions preferably contain at least one surfactant of good wetting ability. This is not intended to imply that any wetting agent will give a suitable foam, and we find that careful selection is desirable in order to produce, in particular, the necessary physical properties of the foam. The surfactant is preferably an addition product of one or more molecules of ethylene oxide and a molecule of an alcohol, amide, acid, amine, or phenol, characterized by including an aliphatic chain of between six and twenty-two carbon atoms. An example of the compositions which we fined to be of value for the present invention is:

Brij 58, a polyoxyethylene cetyl ether, containing 20 ethylene oxide units, made by Honeywell-Atlas Corp.	8.0%
Myristyl alcohol	8.0%
Water to 100%,	
Packed as aqueous solution,	92 parts
Propellant (a mixture of dichlorodifluoromethane and dichlorotetrafluoroethane in the weight ratio of 40:60)	8 parts.

This composition is particularly valuable in that it produces a good foam even when the pH is varied, by the addition of an acid or a base or a buffer mixture, between about 5.0 and about 10.0 units.

The following Examples in which the percentages are by weight, illustrate the invention.

Example 1

A liquid composition was prepared consisting of 7.0% of stearic acid, 3.0% of triethanolamine, 5.0% of propylene glycol 0.2% of mineral oil, 0.2% of Carbopol 940 (a carboxypolymethylene made by Stein Ltd.; Carbopol is a registered Trade Mark), 0.05% of 5 - nitro - 2 - furaldehyde semicarbazone and water to 100%. 158 g. of this liquid composition together with 12 g. of a mixture of dichlorodifluoromethane and dichlorotetrafluoroethane in the weight ratio of 40:60 as propellant was introduced into a 6 oz. tinplate can fitted with a valve having a discharge orifice 0.018 of an inch in diameter. On operating the valve a pale yellow, smooth, stable foam was formed.

Example 2

Example 1 was repeated but using 1.5% of 5 - nitro - 2 - furaldehyde semicarbazone. On operating the valve a deep speckled yellow, smooth, stable foam was obtained.

Example 3

In this Example a 6 oz. tinplate can having two compartments and fitted with a valve as illustrated in Figures 1 and 2 was used. The outer compartment contained 125 g. of a liquid composition consisting of 5% of Brij 58 (a polyoxyethylene cetyl ether containing 20 ethylene oxide units), 5% of myristyl alcohol and 90% water, and 14.4 g. of the propellant used in Example 1. The inner compartment contained 35 g. of a 0.3% dispersion of 5 - nitro - 2 - furaldehyde semicarbazone in a 5% aqueous Brij 30 (a polyoxythylene lauryl ether containing 4 ethylene oxide units, manufactured by Honeywell-Atlas Corp.) solution.

Example 4

Example 3 was repeated but using Tween 21 (a sorbitan laurate ester containing 4 ethylene oxide units made by Honeywell Atlas Corp.; Tween is a registered Trade Mark) in place of Brij 30.

Example 5

Example 3 was repeated but omitting the Brij 30.

In Examples 3 to 5 all the foams were expelled satisfactorily on operating the valve. They were found to be stable and uniform in colour. The foam of Example 5 was more mobile than the other two foams.

Example 6

In this Example an 8 oz. bottle fitted with a valve having two discharge orifices each of 0.02 of an inch in diameter was used. The contents consisted of 170 grams of a liquid composition of 8.3% of Brij 58, 8.3% of myristyl alcohol, 83.2% of water and 0.2% of 5 - nitro - 2 - furaldehyde semicarbazone with 14 g. of the same propellant as in Example 1. On operating the valve a wet, stable foam having a pH of 5.1 was slowly expelled.

Example 7

Example 6 was repeated but using 2.3% each of Brij 58 and myristyl alcohol and 95.2% of water. Similar results to those of Example 6 were obtained but the foam was very wet and the pH was 5.2.

Example 8

In this Example a can of the kind used in Example 3 was employed. The outer compartment contained 125 g. of a liquid composition consisting of 10.3% of Brij 58, 10.3% of myristyl alcohol, 79.25% of water and 0.15% of the sodium salt of 2 - sulphanilamidopyrimidine, and 14 g. of the propellant used in Example 1. The inner compartment contained 0.05 g of silver nitrate and water to 35 g. On operating the valve a stable foam was obtained.

Example 9

In this Example a can of the kind used in Example 1 was employed. The can contained 156 g. of a liquid composition consisting of 8.0% of Brij 58, 8.0% of myristyl alcohol, 0.2% of the silver salt of 2 - sulphanilamidopyrimidine and 83.8% of water and 14 g. of the propellant used in Example 1. The pH of the concentrate was 4.02. On operating the valve a thick, white, slightly curdy foam was obtained.

Example 10

In this Example a can of the kind used in Example 3 was employed. The outer compartment contained 125 g. of a liquid composition consisting of 8% of Brij 58, 8% of myristyl alcohol and 84% of water, and 14 g. of the propellant used in Example 1. The inner compartment contained 35 g. of a 1% aqueous solution of silver nitrate. The pH of the liquid composition was 4.0. On operating the valve a wet and creamy foam having a pH of 4.2 was formed. The Example was repeated adding triethanolamine to produce a liquid composition having a pH value of 7.3, which gave a foam having a pH value of 6.8. A stable foam was obtained.

Example 11

Example 10 was repeated but using 35 g. of a 5% solution of silver nitrate. A stable

foam was formed which developed a dark brown skin on standing in the air.

Example 12

In this Example a 2½ oz. aluminium can fitted with a valve having two discharge orifices each of 0.02 of an inch in diameter was used. The can contained 50 g. of a liquid composition consisting of 7.5% of Brij 58, 7.5% of myristyl alcohol, 80% of water and 5.0% of *o* - amino - *p* - toluene - sulphonamide acetate, and 4 g. of the propellant used in Example 1. On operating the valve a shiny, white, stable foam was obtained.

All the above foams were effective, to varying degrees, in the control of *Pseudomonas aeruginosa*.

As will be recognised by those skilled in the art, the above Examples can be modified by the addition of thickeners, surfactants, oils, and waxes, and the properties of the foams may be further modified by changes in the ratio of aqueous solution to propellant.

WHAT WE CLAIM IS:—

1. A container of antiseptic for the treatment of burns and scalds by topical application, containing a topically acceptable antiseptic active against *Pseudomonas aeruginosa*, a pressurising agent and at least one surfactant admixed with water, said container comprising an outlet, and valve means operable to allow discharge of the contents of the container through said outlet in the form of a foam which is effective in the control of *Pseudomonas aeruginosa* at the site of a burn or scald.

2. A container of antiseptic for the treatment of burns and scalds by topical application, comprising a first compartment containing a pressurising agent and at least one surfactant admixed with water, a second compartment containing a topically acceptable antiseptic active against *Pseudomonas aeruginosa* or a substance which will react with a substance contained in said first compartment to form a desired antiseptic, said second compartment containing a pressurising agent and/or being collapsible under the pressure of the pressurising agent contained in said first compartment, an outlet from the container, and valve means operable to put both compartments in communication with the outlet, operation of said valve means resulting in discharge from said outlet of a foam containing an antiseptic which is effective in the control of *Pseudomonas aeruginosa* at the site of a burn or scald.

3. A container according to either claim 1 or 2, which does not contain any soap.

4. A container according to any one of the preceding claims, wherein the antiseptic is a salt of *o* - amino - *p* - toluenesulphonamide.

5. A container according to claim 4, wherein said salt is a water-soluble salt.

6. A container according to claim 5, wherein said salt is an acetate of a hydrochloride.

7. A container according to claim 5, wherein said salt is a lactate or tartrate.

8. A container according to any one of claims 4 to 7, wherein the antiseptic is present in an amount of from 0.5% to 5.0% by weight, based on the weight of material dispensed from the container on operation of the valve.

9. A container according to claims 1 to 3, wherein the antiseptic is 5 - nitro - 2 - furaldehyde semicarbazone.

10. A container according to claim 9, wherein the antiseptic is present in an amount of from 0.05% to 1.5% by weight, based on the weight of material dispensed from the container on operation of the valve.

11. A container according to any one of claims 1 to 3, wherein the antiseptic is the silver salt of 2 - sulphanilamidopyrimidine.

12. A container of antiseptic for the treatment of burns and scalds by topical application, comprising a first compartment containing a salt of 2 - sulphanilamidopyrimidine, a pressurising agent and at least one surfactant admixed with water, a second compartment containing a silver salt, at least the lining of said second compartment being non-reactive with silver ions, said second compartment containing a pressurising agent and/or being collapsible under the pressure of the pressurising agent contained in said first compartment, an outlet from the container, and valve means operable to put both compartments in communication with the outlet, an operation of said valve means resulting in discharge from said outlet of a foam containing a silver salt of 2 - sulphanilamidopyrimidine which is effective in the control of *Pseudomonas aeruginosa* at the site of a burn or scald.

13. A container according to claim 12, wherein said first compartment contains a sodium, potassium or triethanolammonium salt of 2 - sulphanilamidopyrimidine.

14. A container according to either claim 12 or 13, wherein said second compartment contains silver nitrate or silver acetate.

15. A container according to any one of claims 11 to 14, wherein the silver salt of 2 - sulphanilamidopyrimidine is present in an amount of from 0.2% to 4.0% by weight, based on the weight of material dispensed from the container on operation of the valve.

16. A container according to any one of claims 1 to 3, wherein the antiseptic is a silver compound capable of ionising to provide argentous ions.

17. A container according to claim 16, wherein silver compound is present in an amount of from 0.02% to 2.0% by weight, based on the weight of material dispensed from the container on operation of the valve.

18. A container according to any of the

preceding claims, wherein the surfactant is an addition product of one or more molecules of ethylene oxide and a molecule of an alcohol, acid, amine or phenol, characterised by including an aliphatic chain of between six and twenty-two carbon atoms.

19. A container of antiseptic for the treatment of burns and scalds by topical application, substantially as described herein with reference to any one of the Examples.

20. A method of treating a burn or scald of a non-human animal which comprises applying to the site of the burn or scald a foam containing an antiseptic which is such that the foam is effective in the control of *Pseudomonas aeruginosa* at a site of the burn or scald.

21. A method according to claim 20, wherein the antiseptic is a salt of α - amino - p - toluenesulphanamide.

22. A method according to claim 21, wherein the foam contains 0.5% to 5.0% by weight of the antiseptic.

23. A method according to claim 20, wherein the antiseptic is 5 - nitro - 2 - furaldehyde semicarbazone.

24. A method according to claim 23, wherein the foam contains 0.05% to 1.5% by weight of the antiseptic.

25. A method according to claim 20 wherein the antiseptic is the silver salt of 2 - sulphanilamidopyrimidine.

26. A method according to claim 25, wherein the foam contains 0.2% to 4.0% by weight of the antiseptic.

27. A method according to claim 20, wherein the antiseptic is a silver compound capable of ionising to provide argentous ions.

28. A method according to claim 27, wherein the silver compound is present in a concentration of from 0.02% to 2.0% by weight of silver calculated on the weight of the foam.

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1372721 COMPLETE SPECIFICATION
1 SHEET This drawing is a reproduction of the Original on a reduced scale

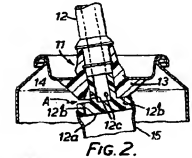

FIG. 2.

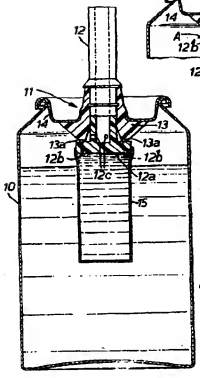

FIG. 1.